REMARKS

Claims 31, 35, and 39 are currently pending.

The Examiner has rejected claims 31 and 35 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner has rejected claim 39 under 35 U.S.C. § 102(b) as allegedly anticipated by Hunger *et al.* (European Journal of Immunology, 1997, 27:255-261) ("Hunger"). The Examiner has rejected claims 31 and 35 under 35 U.S.C. § 103(a) as allegedly obvious over Muruve *et al.* (Transplantation, 1997, 64:542-546) in view of Hunger. The Examiner has also rejected claims 31 and 35 under 35 U.S.C. § 103(a) as allegedly obvious over Muruve in view of Hunger and further in view of Petrik *et al.* (Endocrinology, 1998, 139:2994) ("Petrik"), Russell *et al.* (J Neurobiology, 1998, 36: 455-67) ("Russell"), Symons *et al.* (Proc. Natl. Acad Sci USA, 1995, 92:1714) ("Symons"), or LaCasse *et al.* (Oncogene, 1998, 17:3247-59) ("LaCasse"). For reasons detailed below, the rejections should be withdrawn and claims allowed to issue. Entry of the foregoing amendments is respectfully requested.

Claims 31 and 35 are Definite

The Examiner has rejected claims 31 and 35 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner argues that claims 31 and 35 are indefinite because they recite "step (a)," although neither claim comprises a "step (a)."

Applicants note that claims 31 and 35 have been amended to recite "step (i)" instead of "step (a)," as recommended by the Examiner. This amendment corrects an obvious typographical error. Accordingly, Applicants submit that the Examiner's rejection for indefiniteness has been obviated, and respectfully request that the rejection be withdrawn.

Claim 39 is not Anticipated by Hunger

The Examiner has rejected claim 39 under 35 U.S.C. § 102(b) as allegedly anticipated by Hunger *et al.* (European Journal of Immunology, 1997, 27:255-261) ("Hunger"). The Examiner states that Hunger teaches a transgenic mouse with pancreatic β cells that express a soluble type I tumor necrosis factor alpha (TNF-α) receptor that binds to TNF-α and inhibits TNF-α signaling. The Examiner further asserts that claim 39, in its broadest interpretation, reads on a transgenic mouse pancreatic β cell that comprises a recombinant nucleic acid molecule that encodes and expresses the soluble TNF- α receptor.

Applicants submit that Hunger does not teach all of the limitations of the present invention. Anticipation requires that each and every element of the rejected claim(s) be disclosed in a single prior art reference. See M.P.E.P. § 2131 (8th Ed. Rev. 2, May 2004). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Every element of the claimed invention must literally be present, arranged as in the claim. *Perkin Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 894, 221 USPQ 669, 673 (Fed. Cir. 1984).

Applicants note that Hunger discloses transgenic mice expressing a soluble TNF receptor which neutralizes bioactive TNF-α. See Hunger at page 255, right column. In contrast, claim 39 recites "a soluble type I tumor necrosis factor alpha receptor decoy protein." As defined in the specification, decoy proteins "are capable of competing... for receptor binding but which fail to activate the signaling activity of the receptor." See specification at page 15, lines 4-6 (emphasis added). Thus, the soluble TNF receptor disclosed in Hunger binds to TNF-α, preventing it from binding to the membrane-bound TNF receptor, whereas the soluble type I

tumor necrosis factor alpha receptor decoy proteins of claim 39 bind to the membrane bound TNF receptor, competing with TNF-α. Accordingly, the soluble TNF receptor of Hunger is not the same as the soluble type I tumor necrosis factor alpha receptor decoy protein of claim 39, and Hunger fails to teach all of the limitations of claim 39.

Based upon the foregoing argument, Applicants submit that claim 39 is not anticipated by Hunger, and respectfully request that the rejection be withdrawn.

Claims 31 and 35 are not Obvious over Muruve in view of Hunger

The Examiner has rejected claims 31 and 35 under 35 U.S.C. § 103(a) as allegedly obvious over Muruve *et al.* (Transplantation, 1997, 64:542-546) ("Muruve") in view of Hunger. The Examiner states that Muruve teaches an adenoviral vector that can be used to express a gene of interest in a pancreatic β cell, which can be transplanted into an individual. The Examiner acknowledges that Muruve fails to teach an adenoviral vector that can be used to deliver and express a soluble TNF-α receptor protein, but asserts that Hunger teaches that expression of a soluble TNF-α receptor protein in mouse pancreatic β cells would reduce β cell dysfunction. The Examiner alleges that it would be obvious to one of ordinary skill in the art to modify Muruve to obtain the present invention.

Applicants submit that the Examiner has not set forth a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See MPEP §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed

combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q2d 1438 (Fed. Cir. 1991).

There is no suggestion or motivation to combine Muruve with Hunger. Muruve only discusses insertion of "foreign proteins" and does not specifically suggest the insertion of a soluble type I tumor necrosis factor alpha receptor decoy protein. See Muruve at pages 545-546. Hunger discloses expression of a soluble TNF-α receptor, which, as noted above, is not the same as a soluble type I tumor necrosis factor alpha receptor *decoy* protein. Accordingly, there is no suggestion or motivation to use the adenovirus vector of Muruve to insert a soluble type I tumor necrosis factor alpha receptor *decoy* protein into β cells.

A person of ordinary skill in the art would not have a reasonable expectation of success by combining Muruve and Hunger. As noted above, Hunger is directed to transgenic mice which systemically express a soluble TNF-α receptor throughout the mice, and results in "consistently high expression" of the soluble TNF-α receptor in the sera of the transgenic mice. In contrast, the present invention is directed to a soluble type I tumor necrosis factor alpha receptor decoy protein which is expressed only in the β-cells. A person of ordinary skill in the art would not be able to reasonably predict that the method of Hunger would work if expression was changed from a soluble TNF-α receptor to a soluble type I tumor necrosis factor alpha receptor *decoy* protein and if expression was limited to the β cells. See MPEP § 2143.02 ("At least some predictability is required" to show a reasonable expectation of success). Accordingly, due to the lack of predictability, a person of ordinary skill in the art would not have a reasonable expectation of successfully combining Muruve and Hunger.

The references cited by the Examiner, alone or in combination, do not teach all of the limitations of the present invention. The Examiner acknowledges that Muruve does not teach the delivery of a soluble TNF-α receptor protein. Neither Muruve nor Hunger teach the delivery of soluble type I tumor necrosis factor alpha receptor decoy protein. As noted above, a soluble TNF-α receptor protein is not equivalent to a soluble type I tumor necrosis factor alpha receptor decoy protein. Accordingly, Muruve and Hunger, alone or in combination, do not teach all of the limitations of the present invention.

Applicants submit that the Examiner has failed to establish a prima facie case of obviousness, because Muruve and Hunger do not teach all of the limitations of the present invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 31 and 35 are not Obvious over Muruve in view of Hunger, Petrik, Russell, Symons, or LaCasse

The Examiner has rejected claims 31 and 35 under 35 U.S.C. §103(a) as allegedly obvious over Muruve in view of Hunger, and further in view of Petrik *et al.* (Endocrinology, 1998, 139:2994) ("Petrik"), Russell *et al.* (J Neurobiology, 1998, 36: 455-67) ("Russell"), Symons *et al.* (Proc. Natl. Acad Sci USA, 1995, 92:1714) ("Symons"), or LaCasse *et al.* (Oncogene, 1998, 17:3247-59) ("LaCasse"). The Examiner states that Muruve and Hunger suggest methods comprising introducing into a β cell a nucleic acid molecule encoding an inhibitor of apoptosis, *i.e.*, a soluble type I TNF alpha receptor decoy protein, but acknowledges that the two references do not teach the use of IGF-I, IGF-II, NF-AT, STAT-6 or IL-1ra (IRAP). The Examiner asserts that these molecules are well known anti-apoptotic molecules (as taught by the remaining cited references) and it would have been obvious to one of skill in the art to

combine the teachings of Muruve and Hunger with any of the other cited references to obtain the claimed invention.

Applicants submit that the Examiner has not set forth a *prima facie* case of obviousness. There is no suggestion or motivation to combine Muruve and Hunger with Petrik, Russell, Symons, or LaCasse. The Examiner asserts that the motivation is provided by Muruve, "who teaches the general principle that apoptosis inhibitors can be used as gene therapeutic agents." The Examiner has not cited, nor can the Applicants locate, any support for this statement; there is, in fact, no discussion of apoptosis in Muruve. At best, Muruve discusses the "potential for applying gene therapy in transplantation," and that the disclosed adenoviral vector does not cause islet destruction; Muruve makes no mention of apoptosis inhibitors. See Muruve at page 545. In addition, contrary to the Examiner's assertion, Hunger does not teach the use of apoptosis inhibitors generally, but teaches protection against "pathological conditions mediated by TNF release," and emphasizes the role of TNF-α in autoimmune destruction of β cells via infiltration and adhesion of lymphocytes. See Hunger at pages 255 and 260. Similarly, Petrik, Russell, Symons, and LaCasse do not provide any suggestion or motivation to insert apoptosis inhibitors into β cells, or that the apoptosis inhibitors would be interchangeable with a TNF-α neutralizing agent. Petrik is directed towards the pattern of expression of IGF-I and IGF-II, and does not discuss their mechanism of action. See Petrik at page 2999-3000 and 3003. Russell is directed towards the inhibition of apoptosis in neurons by IGF-I when neuron growth factor has been withdrawn. See Russell at page 455. Symons is directed towards the binding of IL-1R to IL-1. See Symons at page 1714. LaCasse is primarily directed to the role of various apoptosis inhibitors in oncogenesis and does not address apoptosis inhibitors in islet cells; in fact, LaCasse states that different apoptosis inhibitors act in a "cell type specific" manner, and that "what is

observed in one system may not hold true for another." See LaCasse at abstract and at page 3250. Thus, Petrik, Russell, Symons, and LaCasse do not provide any suggestion or motivation to insert the apoptosis inhibitors into β cells to treat diabetes; indeed, Russell, Symons, and LaCasse do not reference β cells or diabetes at all. Similarly, Petrik, Russell, Symons, and LaCasse do not provide any suggestion or motivation that they would be interchangeable with a TNF-α neutralizing agent. Accordingly, based upon the disclosure in these references, a person of ordinary skill in the art would therefore not be motivated combine Muruve and Hunger with Petrik, Russell, Symons, or LaCasse.

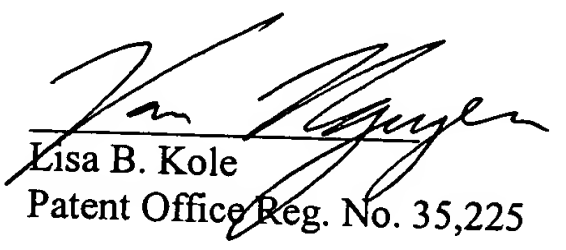
Combination of the cited references does not provide a person of ordinary skill in the art a reasonable expectation of success. As noted above, Muruve does not provide any guidance regarding apoptosis inhibitors, and Hunger is directed to a soluble TNF-α receptor to neutralize bioactive TNF-α. See Hunger at pages 259-260. As discussed above, Petrik, Russell, Symons, and LaCasse do not provide information linking the mechanism of action of the apoptosis inhibitors with TNF-α. Based upon those references, a person of ordinary skill in the art would not be able to predict the effectiveness of inserting the apoptosis inhibitors of Petrik, Russell, Symons, and LaCasse into β cells, as Muruve does not discuss apoptosis inhibitors. Similarly, a person of ordinary skill in the art would not be able to predict the effectiveness of replacing the TNF-α neutralizing compound of Hunger with the apoptosis inhibitors, because the function of the apoptosis inhibitors is not disclosed to be associated with TNF-α. Accordingly, due to the lack of predictability, a person of ordinary skill in the art would not have a reasonable expectation of success of combining Hunger and Muruve with Petrik, Russell, Symons, or LaCasse. See MPEP § 2143.02 ("At least some predictability is required" to show a reasonable expectation of success).

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, because there is no motivation or suggestion to combine the cited references or a reasonable expectation of success of combining the references. Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicant believes that the inventions described and defined by claims 31, 35, and 39 are patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claim is requested. An early allowance is earnestly sought.

Respectfully submitted,



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